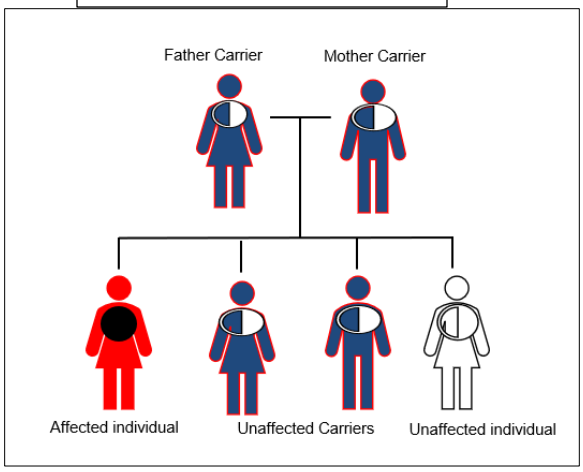
HAVING CHILDREN WHEN YOU HAVE POMPE DISEASE

Pompe disease is a genetic disease. Genetic diseases are caused by abnormalities in gene(s) or chromosomes. Genetic diseases are passed from parents to their children through genes. Genes are basic units of heredity and consist of small segments of DNA that contain instructions for processes and structures in the human body, as well as features that make a person unique. Some genes control traits and features such as gender, height, and eye color. Other genes control bodily processes, such as making the enzymes that help the body function.

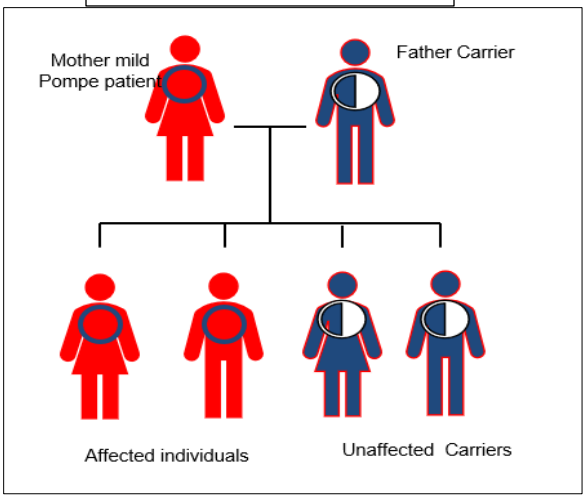
Pompe disease is caused by a genetic mutation that blocks the production of an enzyme (a type of protein) called *acid alpha-glucosidase.* This can lead to muscle damage throughout the body. You can only get Pompe disease when you inherit 1 copy of the defective gene from each parent, as shown in this diagram. This is called *autosomal recessive inheritance.* If both parents are carriers of Pompe, there is a 1 in 4 chance they will have a child with Pompe. For this reason, men and women with a family history of Pompe disease may be concerned about having children.

Two Carriers



The chance of having a child with Pompe increases if one of the parents has Pompe Therefore, partners of people with Pompe disease may want to know if they are carriers of the defective gene as well as a carrier and a Pompe patient have a child there is a 50% chance the baby will have Pompe.

Patient and a Carrier



Women who have Pompe disease may also worry about the health risks of becoming pregnant because of the added strain that pregnancy may put on their bodies and health.

If you are thinking about having children, it is important to be aware of both the chances of passing on the disease, and the problems that could arise before, during, and after pregnancy. If you already have children, you may want to know their risk for having the disease or passing it on. This brochure talks about some of the issues you will want to think about. It also describes the tests that can help predict whether your baby will be affected by Pompe disease.

Q: What is human genetics and what does it have to do with Pompe disease?

A: Human genetic makeup is encoded into complex chemical structure called DNA (short for deoxyribonucleic acid). DNA molecules form the basis of structures called chromosomes. Every person has 46 chromosomes, grouped into 23 pairs, which are found inside cell's nucleus. Each chromosome is itself divided into thousands of smaller segments, called genes.

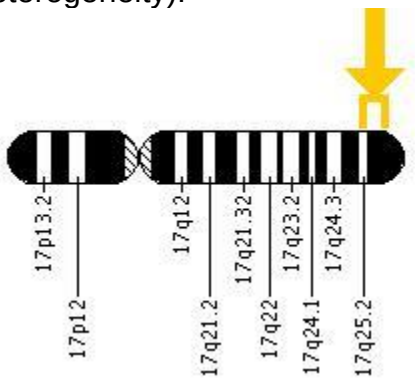
Among the 23 pairs of chromosomes, one pair, called sex chromosomes, determines a person's gender. The other 22 pairs, called autosomes, determine all other non-gender-related traits.

Because genes are a part of chromosomes, they also come in pairs - during reproduction, each parent passes on a copy of half of their genetic material to their offspring.

Each gene pair works together to control a specific function or activity within the cell. Some have relatively small significance, such as defining a person's hair or eye color, while others control important cellular activities, such as the production of vital enzymes needed for healthy functioning.

A gene mutation is a permanent alteration in a gene. Disease results from the gene's inability to produce a protein the body needs for normal functioning. The altered diseases produced by gene mutations can be mild, severely debilitating, or fatal.

The gene that causes Pompe disease is called GAA and is located on chromosome 17, which is an autosomal chromosome. (More on this under the section titled Genetic Heterogeneity).



There are many different defects, or mutations, that can affect the GAA gene. Most people with Pompe disease inherit two different GAA gene mutations, one from each of their parents. Researchers have already identified approximately 500 distinct mutations (although not every one of these always causes Pompe disease), and more continue to be found.

For more detailed information about genetic heterogeneity go to the Pompe Center, Erasmus MC Rotterdam website

Q: What does it mean to be a carrier of Pompe disease?

A: The term "carrier" when used in relation to Pompe describes a person who could potentially pass on a disease to their children but does not actually have Pompe themselves. This is because carriers of Pompe disease have one bad copy of the GAA gene, and Pompe patients have two. The one good copy of the GAA gene that carriers have allows for the production of enough enzymes to keep cells functioning properly. A carrier's enzyme activity is usually somewhat lower than normal, but they usually do not experience any symptoms.

Q: Does Pompe Disease affect one ethnic group more than others?

A: Research has shown that Pompe disease is pan-ethnic—it occurs in people of all ethnicities and races. There does appear to be a slightly higher incidence rate in certain groups:

- In infants, the disease has a higher frequency among African-Americans and people from southern China and Taiwan.
- Among adults, the disease has a higher frequency in the Netherlands.

In addition, specific gene mutations have been found to be more common in certain ethnic groups or nationalities. It's still unclear exactly why these higher frequencies exist in certain groups, although the disease's genetic basis and family inheritance patterns are likely major contributing factors.

Q: How do you inherit Pompe disease?

A: Pompe disease is a genetic disorder, passed down from parent to child in an autosomal recessive manner. Autosomal recessive diseases are relatively rare, because to get Pompe disease you must inherit one bad copy of the gene from both parents, not from just from one parent. So that means both parents must have at least one bad copy of the gene.

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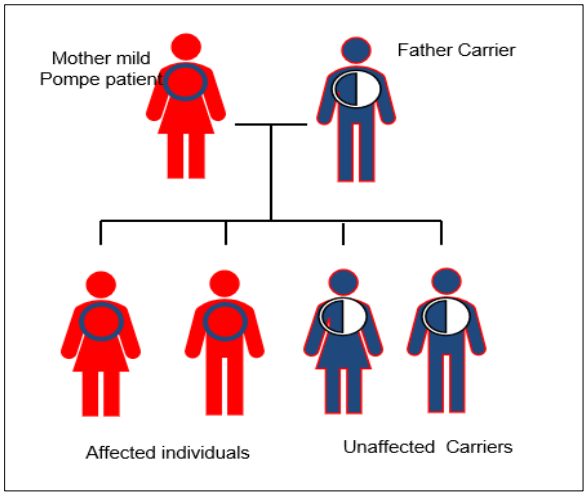
Inheritance Scenarios:

- If one parent has Pompe disease and the other parent is unaffected:
  - There is a 100% chance the child will be a carrier. The parent with Pompe disease has two bad copies of the gene, so the child will always get one bad copy of the gene from that parent, and one good copy of the gene from the parent who is unaffected.
- If one parent has Pompe disease, and the other parent is a carrier:
  - There is a 50% chance the child will get Pompe disease. The child will get one bad copy of the gene from the parent with Pompe disease, and a 50% chance of getting a second bad copy of the gene from the parent who is a carrier.
  - There is a 50% chance the child will be a carrier. The child will get one bad copy of the gene from the parent with Pompe disease, and a 50% chance of getting one good copy of the gene from the parent who is a carrier.



- If one parent is a carrier of Pompe disease and the other parent is unaffected:
  - There is no chance the child will get Pompe disease. The child will always get one good copy of the gene from the parent who is unaffected and 50% chance of getting a second good copy of the gene from the parent who is a carrier.
  - There is a 50% chance the child will be a carrier. The child will always get one good copy of the gene from the parent who is unaffected and 50% chance of getting one bad copy of the gene from the parent who is a carrier.

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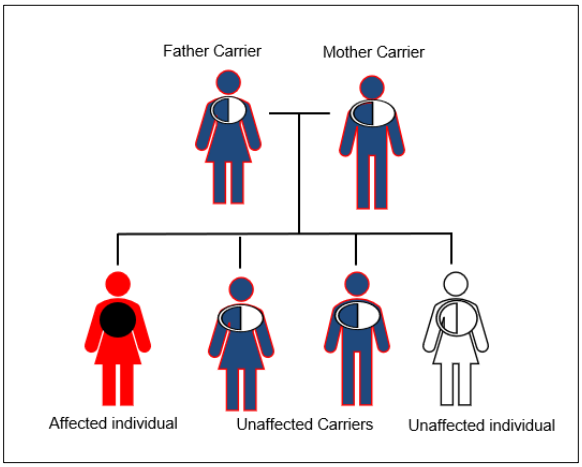
- If both parents are carriers, each child born to them has a:
  - 25% chance of having the disease
  - 50% chance of being a carrier of the disease
  - 25% chance of neither having the disease nor being a carrier of the disease



Q: I have a family history of Pompe. Are there tests to determine if my partner and I are Pompe carriers?

A: Preconception testing is available in many countries to see if parents carry the Pompe Gene. Preconception testing should be done under the guidance of a Genetic Councilor This involves taking a sample of saliva or blood, separating the DNA from the cells, and then looking for the specific mutations that are known to cause Pompe disease. Molecular testing of DNA mutations is possible because more than 500 mutations of the GAA gene have been identified in people with Pompe disease. Some of these mutations are limited to particular ethnic groups.

Mutation analysis is the only way to identify carriers, who do not have the disease, but "carry" the gene defect and may pass it on to their own children - it's particularly important to identify carriers within families with a history of the disease. However, it should be understood that preconception testing may not be definitive as not all mutations for Pompe have been identified.

Q: I am currently pregnant. Is there a way to find out if my unborn child has Pompe disease?

A: Yes, there are prenatal screening tests that can be done early in pregnancy to see if your fetus (unborn child) is affected with Pompe disease.

Chorionic villus (tiny finger-shaped growths found in the placenta) *sampling,* or CVS, is done between the 10th and 12th week of pregnancy. This test involves taking a small sample of tissue from the growing placenta (an organ that connects the developing fetus to the uterine wall to allow nutrient uptake, waste elimination, and gas exchange via the mother's blood supply) and measuring enzyme activity.

Prenatal testing is also available by enzyme analysis in amniocytes (amniocyte is a cell

of a fetus which is suspended in the amniotic fluid) taken from the amniotic fluid (amniocentesis). An amniocentesis can be performed as early as the 12th week of pregnancy and can provide results as quickly as a few days. This test checks for enzyme activity and allows for DNA analysis by testing cells taken from fluid in the womb.

DNA testing may also be done to compare the DNA from the fetus with the DNA of the parents or an affected brother or sister.

The results of these prenatal tests can help guide choices about the pregnancy and prepare for the baby's arrival.

Q. There is a history of Pompe in my family and my healthcare provider has advised me to get genetic counseling before I get pregnant. What is a Genetic Counselor?

A: Genetic counselors are health care professionals with unique specialized graduate degrees and experience in the areas of both medical genetics and counseling. Genetic counselors work as members of a health care team, providing risk assessment, education and support to individuals and families at risk for, or diagnosed with, a variety of inherited conditions, like Pompe disease. Genetic counselors also interpret genetic testing, provide supportive counseling, and serve as patient advocates.

If you or a family member has Pompe disease, or a carrier for Pompe disease, genetic counseling can help you understand your chances for having a baby with the disease. Meeting with a genetic counselor **before you get pregnant** will help you sort out all the issues that may affect your decision to have children:

A genetic counselor will be able to:

- Explain family inheritance patterns and identify potentially at-risk individuals.
- Provide balanced information about what genetic testing involves, in order to support decisions about who to test
- Help family members cope with positive test results.
- Provide guidance on genetic issues such as family planning and prenatal testing.

If you are already pregnant the genetic counselor can talk to you about prenatal testing for your unborn child. Should you choose to go ahead with genetic testing; the genetic counselor will help you make appointments for the tests and provide the support you need once you get the test results back. For example, if you find out your unborn child is affected by Pompe disease, the genetic counselor can help you explore your options and cope with the difficult choices ahead of you. Since the process of getting tested and waiting for results takes time, it is important to seek genetic counseling as early as possible.

Q: Should I be treated with Enzyme replacement if I become pregnant?

A: Please see links below for clinical articles on Enzyme Replacement and Pregnancy Ref 1 and 2

Q: Can I get pregnant if I have Pompe disease?

A: Pompe disease does not appear to affect fertility (the ability to conceive a child). Women diagnosed with Pompe disease also do not seem to have a higher risk for miscarriage (loss of the pregnancy).

Q: I have Pompe disease and I want to start a family. How will pregnancy affect my health?

A: Although having Pompe disease should not affect your ability to get pregnant or carry a pregnancy to term; there are some health concerns to be aware of, especially if you are severely affected. You should talk with your treating specialist about things like weight gain, Respiratory changes, Delivery and Recovery.

Where to Learn More: Please see the more information section

Ref 1 Genetic counseling in Pompe disease
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298105/?report=classic
Antonella Taglia, Esther Picillo, Paola D'Ambrosio, Maria Rosaria Cecio, Emanuela Viggiano, and Luisa Politano

Ref 2 Pompe disease treated with enzyme replacement therapy in pregnancy
https://pubmed.ncbi.nlm.nih.gov/33035415/
Zoltán Grosz [1], Katalin Visy Várdi [2], Judit Mária Molnár [1]